Aswan University Medical Journal, volume 4 / No.1/ June 2024 (224-231) - Online ISSN: **2735-3117**

ORIGINAL ARTICLE

Flaring of Arthritis in Rheumatoid Arthritis Patients after COVID-19 Vaccination

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ABSTRACT

Keywords: Rheumatoid arthritis, COVID-19 vaccination, arthritis flare

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Background: Rheumatoid arthritis (RA) is the most common inflammatory arthritis that can cause damage to the joints. **Aim:** To study the prevalence of arthritis flare among rheumatoid Arthritis patients after (2-doses) SARS–CoV-2 mRNA vaccination in Aswan university hospital. **Patients and methods:** This prospective study was conducted on 150 rheumatoid arthritis patients diagnosed according to ACR/EULAR 2010 rheumatoid arthritis classification criteria and ACR 1987 classification criteria of rheumatoid arthritis was recorded in the rheumatology out-patient clinic in Aswan University Hospital form the period from September 2021 to August 2022. **Results:** There was statistically significant increase in arthralgia, ESR and DAS 28 score after vaccination (p-Value <0.05), while there was no statistically significant difference in arthritis score before and after vaccination (p-Value >0.05). **Conclusion:** Pre-vaccination disease activity evaluation revealed arthralgia mean of 0.53 ± 0.78, ranging from 0 to 3, and arthritis mean of 0.08 ± 0.3, ranging from 0 to 2. For DAS 28, the mean was 2.42 ± 0.22, ranging from 1.06 to 2.6. Following the COVID-19 vaccine, 84.7% of RA patients used HCQ, 66.7% used MTX, and 22.7% used steroids. Only 6 (4% of biologically treated patients).

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis (Thomas & Vassilopoulos, 2020) that can cause damage to the joints. It can also present with extra-articular manifestations, affecting other major organs. [1] Infections are the most important comorbidities associated with increased morbidity and mortality. [2]

Corona viruses represent a major group of viruses mostly affecting human beings through zoonotic transmission. In the past two decades, this is the third instance of the emergence of a novel coronavirus, after the severe acute respiratory syndrome (SARS) in 2003 [3] and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. [4]

In December 2019, a novel outbreak of a new strain of coronavirus infection emerged in Wuhan, China the SARS-CoV-2 or the Covid-19, The disease was declared as a pandemic in early March 2020. [5]

To date, the main tools for controlling COVID-19-related mortality are vaccines. The new methods in the development of vaccines (mRNA and viral vectors) initially caused concern in the population given the lack of previous experience with this technology; however, clinical trials showed adequate levels of efficacy and safety in the included population. [6]

In December 2020, 2 messenger RNA (mRNA)–based COVID-19 vaccines (mRNA-1273 and BNT162b2) were recommended for use by the advisory committee on immunization practices. [7]

However, these studies did not include patients with autoimmune diseases, which have not made it possible to establish a level of efficacy and/or safety for this group of patients (considering the immunological alteration inherent to these diseases, immunosuppressive therapy, and the possible impact on disease activity). [8]

The aim of this study was to study the prevalence of arthritis flare among rheumatoid Arthritis patients after (2-doses) SARS–CoV-2 mRNA vaccination in Aswan university hospital.

PATIENTS AND METHODS

This prospective study was conducted on 150 rheumatoid arthritis patients diagnosed according to ACR/EULAR 2010 rheumatoid arthritis classification criteria [9] and ACR 1987 classification criteria of rheumatoid arthritis [10] was recorded in the rheumatology out-patient clinic in Aswan University Hospital form the period from September 2021 to August 2022.

Inclusion criteria: Patients aged > 18years old, both sex, confirmed clinical diagnosis of RA of ≥ 6-month duration, RA Patients with sustained clinical remission for more than 3 month and RA Patients which are fully COVID-19 vaccinated (two completed doses).

Exclusion criteria: Age < 18 years, RA Patients not controlled on treatment in the last 3 month and RA Patients not vaccinated or receiving only one dose of vaccine

Data collection and methods:

The study was conducted through a patient-reported questionnaire regarding demographic characteristics (age and sex), RA diagnosis, new onset symptoms of RA, any changes in the laboratory or radiological investigations of the patients and immuno- modulatory regimen. All patients will be subjected to complete history taking, complete general examination, and detailed rheumatological examination.

The 150 patients were received the SARS-COV2 Vaccine (Vero cell), inactivated (Sinopharm). This vaccine was adjuvanted fully liquid, inactivated, preservative-free suspension in vials and non-AD prefilled syringes. All patients received two doses of the vaccine; each single dose is (0.5ml). The 2 doses at recommended interval of 3 to 4 weeks: Dose 1: at the start date. Dose 2: 21 to 28 days after the first dose. Then all patients were investigated and clinically assessed within 14 days of the second dose of the vaccine

Clinical and laboratory assessment: Complete blood count (CBC)**,** C-reactive protein (CRP)**,** erythrocyte sedimentation rate(ESR) and presence of rheumatoid factor (RF) and anti-citrullinated cyclic peptides antibodies(anti-CCP)

Ethical considerations: Approval of the ethical committee board was obtained. Each participant had written informed consent before study enrollment and was told about all steps of the study. The confidentiality of all included participants were considered. All participants had the right to leave at any stage of the study if they want.

Data Management and Analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistically package for Social Science (SPSS 25). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Descriptive statistics: Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non-parametric numerical data. Frequency and percentage of non-numerical data. Analytical statistics: Paired t-test was used to assess the statistically significance of the difference between two means measured twice for the same study group. Wilcoxon signed rank test was used assess the statistically significance of the difference of an ordinal variable (score) measured twice for the same study group. P- value: level of significance: P>0.05: Non significant (NS) and P< 0.05: Significant (S).

RESULTS

Table 1 shows that mean age of the studied group was 48.01 ± 11.33 years ranged from 21 to 74 years old. 89.3% of patients were females and 10.7% were males. The mean of disease duration was 5.17 ± 3.62 years ranged from 0 to 15 years.

Table 2 shows disease activity assessment before vaccination among the study group, mean of arthralgia was 0.53 ± 0.78 and ranged from 0 to 3, while mean of arthritis was 0.08 ± 0.3 and ranged from 0 to 2 and mean of ESR was 26.28 ± 9.82 and ranged from 10 to 41. Regarding mean of DAS 28-ESR was 2.42 ± 0.22 and ranged from 1.06 to 2.6.

Table 3 shows the treatment received by the study group, the most frequent treatment used was HCQ by 84.7% followed by MTX 66.7%, while the least frequent treatment was steroids by 22.7%. Only 6 (4%) of patients who received biological treatment.

Table 4 shows the lab investigations done for patients after vaccination, regarding complete blood count mean of Hb (12.04 ± 1.29), RBCs (4.57 ± 0.61), WBCs (5.45 ± 1.48) and PLT (266.59 ± 60.96). According to inflammatory markers mean of ESR was (36.62 ± 17.9). 33.3% of patients were CRP positive.

Table 5 shows disease activity assessment after vaccination among the study group, mean of arthralgia was 1.21 ± 1.7 and ranged from 0 to 11, while mean of arthritis was 0.08 ± 0.34 and ranged from 0 to 3 and mean of ESR was 36.62 ± 17.90 and ranged from 10 to 108. Regarding mean of DAS 28-ESR was 2.89 ± 0.68 and ranged from 1.6 to 5.48.

Table 6 shows difference of DAS before and after Covid-19 vaccination, there was statistically significant increase in arthralgia, ESR and DAS 28 score after vaccination as p-Value <0.05, while there was no statistically significant difference in arthritis score before and after vaccination as p-Value >0.05.

Table 1: Demographic data for the whole study group.

		Mean / N	SD / %	Median (IQR)	Range
Age		48.01	11.33	49 (39 - 57)	(21 - 74)
Sex	Female	134	89.3%		
	Male	16	10.7%		
Marital status	Yes	135	90.0%		
	No	15	10.0%		
Disease duration (years)		5.17	3.62	4 (2 - 7)	(0 - 15)

Table 2: Disease activity assessment before vaccination for the whole study group.

	Mean	SD	Median (IQR)	Range
Arthralgia	0.53	0.78	0 (0 - 1)	(0 - 3)
Arthritis	0.08	0.30	0 (0 - 0)	(0 - 2)
ESR	26.28	9.82	28.5 (18-36)	(10 – 41)
DAS 28_ESR	2.42	0.22	2.46 (2.38 - 2.58)	(1.06 - 2.6)

Table 3: Treatment for the whole study group.

		N	%
Steroid	No	116	77.3%
	Yes	34	22.7%
MTX	No	50	33.3%
	Yes	100	66.7%
HCQ	No	23	15.3%
	Yes	127	84.7%
LFN	No	110	73.3%
	Yes	40	26.7%
Biologics	No	144	96.0%
	Simponi	4	2.7%
	Ramicade	1	0.7%
	Enabril	1	0.7%

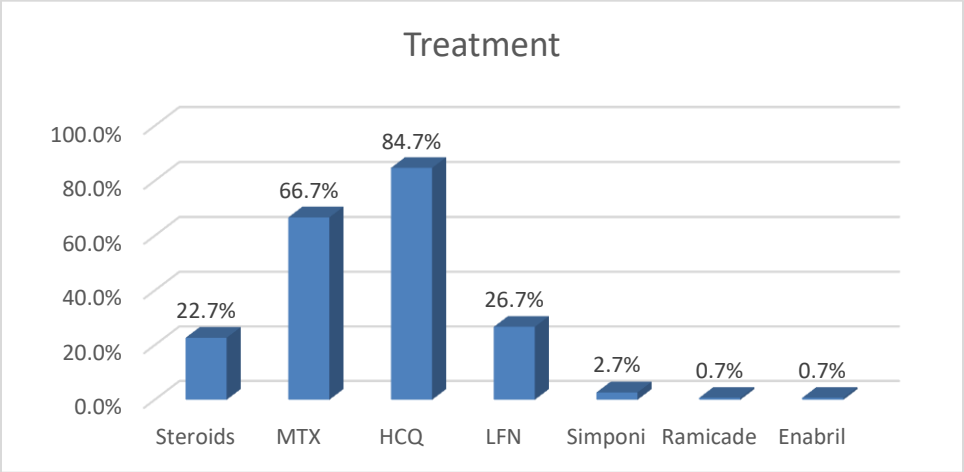

Figure (1): Shows treatment received by the whole study group

Table 4: Lab investigations after vaccination for the whole study group.

		Mean / N	SD / %	Median (IQR)	Range
HB		12.04	1.29	11.85 (11.1 - 12.6)	(9.8 - 16.4)
RBC		4.57	0.61	4.5 (4.2 - 4.8)	(3.6 - 6.5)
WBC		5.45	1.48	5.4 (4.4 - 6.2)	(2.5 - 10.9)
PLT		266.59	60.96	267 (228 - 316)	(137 - 416)
ESR		36.62	17.90	35 (24 - 47)	(10 - 108)
CRP	Negative	100	66.7%		
	Positive	50	33.3%		

Table 5: Disease activity assessment after vaccination for the whole study group.

	Mean	SD	Median (IQR)	Range
Arthralgia	1.21	1.70	1 (0 - 2)	(0 - 11)
Arthritis	0.08	0.34	0 (0 - 0)	(0 - 3)
ESR	36.62	17.90	35 (24 - 47)	(10 - 108)
DAS 28_ESR	2.89	0.68	2.71 (2.38 - 3.32)	(1.6 - 5.48)

Table 6: Disease activity assessment before and after vaccination for the whole study group.

	Before	After	Test of significance	
	Median (IQR) Mean ± SD	Median (IQR) Mean ± SD	p-Value	Sig.
Arthralgia	0 (0 - 1)	1 (0 - 2)	<0.001	S
Arthritis	0 (0 - 0)	0 (0 - 0)	1.00	NS
ESR	28.5(18-36)	35(24-47)	< .00001	S
DAS 28_ESR	2.42 ± 0.22	2.89 ± 0.68	<0.001	S

DISCUSSION

In our current study we found that the mean age of the studied group was 48.01 ± 11.33 years ranged from 21 to 74 years old. 89.3% of patients were females and 10.7% were males. The mean of disease duration was 5.17 ± 3.62 years ranged from 0 to 15 years.

In supporting our results **Li et al, [11]** who aimed to investigate the relationship between COVID-19 full vaccination (two completed doses) and possible arthritis flare. They found that among 5493 patients with RA there was CoronaVac: 671 with Male (N (%) was 194 (28.9%) and female was 477 (71.08%) and the Age (mean (SD) was 59.52 (11.04).

The mean of arthralgia was 0.53 ± 0.78 and ranged from 0 to 3, while mean of arthritis was 0.08 ± 0.3 and ranged from 0 to 2 and mean of ESR was 26.28 ± 9.82 and ranged from 10 to 41. Regarding mean of DAS 28-ESR was 2.42 ± 0.22 and ranged from 1.06 to 2.6.

In line with our results **Geng et al, [12]** they found that according to disease activity assessment before vaccination in RA (n = 98) as regarding DAS28-ESR was 2.35 ± 0.87

In contrast to the presentation of our results **Fong et al, [13]** who aimed to determine prevalence and factors associated with flares post Coronavirus disease 2019 (COVID-19) mRNA vaccination in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA). They reported that disease activity before vaccination was Remission, n (%) in 1093 (46.0), Low disease activity, n (%) in 953 (40.1), Moderate disease activity, n (%) in 290 (12.2) and High disease activity, n (%) in 41 (1.7).

The most frequent treatment used was HCQ by 84.7% followed by MTX 66.7%, while the least frequent treatment was steroids by 22.7%. Only 6 (4%) of patients who received biological treatment.

In supporting our results **Bartels et al, [14]** who aimed to explore the reactogenicity of the BNT162b2 vaccine in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). They found that treatment with Methotrexate was 82 (53.2), Hydroxychloroquine was 2 (1.3), Leflunomide was 14 (9.1) and Number of biologics tried, median 2 (1–3).

In contrast with our results **DiIorio et al, [15]** reported that Most (274/411, 82.0%) were on at least one disease-modifying antirheumatic drug (DMARD) at time of survey. The most common DMARDs were methotrexate (26.5%), antimalarials (26.1%) and tumour necrosis factor inhibitors (15.0%); 27.4% reported glucocorticoid use.

As the lab investigations done for patients after vaccination, regarding complete blood count mean of Hb (12.04 ± 1.29), RBCs (4.57 ± 0.61), WBCs (5.45 ± 1.48) and PLT (266.59 ± 60.96).

According to inflammatory markers mean of ESR (36.62 ± 17.9). 33.3% of patients were CRP positive.

In agreement with our results **Baimukhamedov et al, [16]** they found as investigations for patients after vaccination that there were high levels of RF (170 IU/mL, normal range <18 IU/mL). According to inflammatory markers mean of erythrocyte sedimentation rate (39 mm/h), CRP (10 mg/L, normal <5 mg/L).

We reported in our results as disease activity assessment after vaccination among the study group, mean of arthralgia was 1.21 ± 1.7 and ranged from 0 to 11, while mean of arthritis was 0.08 ± 0.34 and ranged from 0 to 3. Regarding mean of DAS 28-ESR was 2.89 ± 0.68 and ranged from 1.6 to 5.48.

In line with our results **Picchianti-Diamanti et al, [17]** they found that according the disease activity in RA patients Disease activity DAS28crp T0 3.2 (2.5-3.5) and median (IQR) DAS28crp T1 3.2 (2.0-3.5) as RA disease activity was evaluated by clinical examination at T0 (at the time of enrollment) and T1 (after 2 weeks from the second dose).

There was statistically significant increase in arthralgia, ESR and DAS 28 score after vaccination as p-Value <0.05, while there was no statistically significant difference in arthritis score before and after vaccination as p-Value >0.05.

In contrast with our results **Geng et al, [12]** they found that there was no significant in DAS28-ESR and DAS28-CRP before and after vaccination as P-Value was 0.059 and 0.064 respectively

CONCLUSION

Pre-vaccination disease activity evaluation revealed arthralgia mean of 0.53 ± 0.78, ranging from 0 to 3, and arthritis mean of 0.08 ± 0.3, ranging from 0 to 2. For DAS 28, the mean was 2.42 ± 0.22, ranging from 1.06 to 2.6. Following the COVID-19 vaccine, 84.7% of RA patients used HCQ, 66.7% used MTX, and 22.7% used steroids. Only 6 (4% of biologically treated patients).

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